

Immune Network: An Example of Complex Adaptive Systems

Debashish Chowdhury

Physics Department
Indian Institute of Technology
Kanpur 208016, U.P.
India

Abstract: The phenomenon of immunological memory has been known for a long time. But, the underlying mechanism is poorly understood. According to the theory of clonal selection the response to a specific invading antigen (e.g., bacteria) is offered by a specific clone of the cells. Some of the lymphocytes activated during the primary response remain dormant and keep circulating in the immune system for a long time carrying the memory of the encounter and, therefore, these long-lived cells are called memory cells. Proponents of the alternative network theory maintain that the immune response is offered by a "network" of clones in a collective manner. In recent years several possible scenarios of the "structure" and function of the immune network have been considered. We have developed mathematical models for describing the population dynamics of the immunocompetent cells in a unified manner. We have incorporated intra-clonal as well as inter-clonal interactions in a discrete formulation and also studied a continuum version of this model.

1 Introduction:

The latin word "immunitas" is related to the concept of exemption from a service or duty or from civil laws (e.g., "diplomatic immunity" of an ambassador of one country in another). It has been known for more than two thousand years [1] that individuals who recover from a disease become "immune" to it; this is the phenomenon of "acquired immunity". The scientific investigation of immunology, however, began much later when Jenner utilized this phenomenon of "acquired immunity" to develop a vaccine against small pox. The first breakthrough in understanding the mechanism of this remarkable phenomenon was made by Louis Pasteur in 1880. Over the last hundred years we have

collected an enormous amount of information on the "hardware" of the immune system (e.g., the molecules and cells involved) [2, 3, 4] but we understand very little about the "software" that runs it, i.e., the principles governing various immunological processes.

Theoretical immunology [5, 6] deals with the mathematical modelling of immunological processes at various levels, e.g., molecular level, cellular level and the level of cell populations. One of the major aims of theoretical immunology [7, 8] is to predict "macroscopic" properties of the immune system from the properties and interactions among its elementary "microscopic" constituents; this problem is similar to those usually studied by physicists using the techniques of statistical mechanics. Theoretical immunologists develop mathematical models to understand how the immune system evolves over long time scales, how its size and inter-cellular interactions vary with time, how these interactions govern the dynamics of the populations of various types of cells during an immune response to a specific antigen and how it "learns" adaptively about new antigens (i.e., acquires new knowledge) and how it retains the newly acquired knowledge in its "memory" and, finally, how it retrieves information from its memory. Several mathematical models have been developed so far to capture the known immunological phenomena as well as to predict new ones. In this chapter we summarize some of the modern approaches to the mathematical modelling of the immune system and illustrate these with specific examples. We hope that some of the modelling strategy developed for the immune system may find applications in designing artificial immune systems.

2 A brief summary of experimental phenomena to be modelled theoretically:

Millions of different varieties of lymphocytes are known to be produced by the immune system. However, according to the *clonal selection theory*, only a specific type can respond to a specific antigen. This is in sharp contrast to the non-antigen-specific response offered by the macrophages to the antigens. The body seemingly anticipates all the types of antigens it may encounter in the future and prepares accordingly by producing a large variety of lymphocytes. For an antigen-specific response the antigen must be, first of all, properly recognized by the specific lymphocytes. Different types of lymphocytes identify the antigens in different manners. Following the recognition of the antigen, a specific type of lymphocyte, which fit best with the antigen, proliferates rapidly through cell division into a clone (a population of genetically identical cells). The corresponding process is called clonal selection because the antigen selects which lymphocytes must develop into a clone [9].

There are several alternative and complimentary routes of immune response. In a humoral immune response a specific type of B-cell proliferates and the

terminal differentiation of a fraction of this B-cell population leads to plasma cells. These produce antibodies, which react with the antigen and eventually lead to the elimination of the antigen from the host system. The remaining fraction of the proliferating B-cells become dormant and keep circulating in the bloodstream carrying a memory of the encounter with the antigen; the latter variety of the long-lived B-cells are called memory B-cells. In the cell-mediated immune response a specific type of T-cell becomes cytotoxic and kills the antigen directly. Memory of the encounter with the specific antigen is thereafter carried by the corresponding long-lived memory T-cells. The helper T-cells play very crucial roles of regulating the immune response in both routes to immunity. The host carrying the memory cells is said to have acquired immunity against the specific antigen because the presence of the memory cells leads to a quicker and stronger secondary immune response when the host is stimulated again with the same antigen. In fact, this is the basic principle of vaccination. The humoral and cell-mediated routes to immunity are illustrated schematically in fig.1.

Normally, the immune system can distinguish the cells and tissues of the host ("self") from the foreign invaders ("non-self"). A normal immune response (NIR) follows when the population of a foreign antigen in the body exceeds a tolerance level [10]. However, under special circumstances, the immune system mistakenly identifies a part of the host as a "foreign" substance because of some "error" [11]. Then, the immune response that follows against the host is called an auto-immune response (AIR) and such a response can lead to a auto-immune disease.

The human immunodeficiency virus (HIV) is an exceptional invader in the sense that, unlike other foreign antigens, it destroys the helper T-cells of the immune system which are known to be crucial for almost all types of immune response. Therefore, during the late stages of HIV infection the patient's immune system becomes disabled; this is the acquired immune deficiency syndrome (AIDS). Such a patient ultimately succumbs to a secondary infectious agent, rather than to the HIV itself [12].

3 Clonal Selection and Its Mathematical Modelling:

The equations describing the population dynamics of the cells involved in immune response to a specific antigen can be formulated in two different ways. In the discrete approach, the population of each type of cells is modelled by a discrete variable which can take one of only two allowed values: 0 and 1 corresponding to low and high populations, respectively. In this approach, the dynamical equations are written as maps in discrete time. Moreover, the interactions between the various pairs of different cell types are also restricted to have only a few discrete set of allowed values. On the other hand, in the

continuum approach, the populations of the cells, the interactions between the different cell types as well as time are assumed to be real variables, which can vary continuously; the population dynamics of the cells are now given by a set of differential equations.

The continuum approach was followed first by Bell [13, 14], and subsequently by many other investigators, for developing mathematical models of clonal selection. But, since quite often the models are "underdetermined" by the available experimental data, i.e., more than one model can account for the known experimental facts, some authors have, in the recent years, advocated the use of a discrete language as a first step towards the formulation of the quantitative theories [15]. The advantage of a discrete language arises from the fact that the range of allowed values of the variables and the parameters is so narrow that one does not need to adjust too many free parameters to reproduce experimentally known facts. The discrete theories can satisfactorily account for the qualitative features of immune response. The discrete models are not intended to be a substitute for the more realistic continuum description; one can construct the continuum counterpart of the discrete model following well known mathematical prescriptions. The relative advantages and disadvantages of these two approaches have also been discussed in detail in the literature.

3.1 Discrete Models of Clonal Selection

The discrete variable that describes the populations of the cells in the discrete models is sometimes called an "automaton" and a system consisting of such mutually-interacting automata are referred to as "cellular automata" (CA). The concept of CA was introduced by Von Neumann in the context of theories of evolution and, subsequently, analyzed in more detail by Wolfram [16]. The CA are known to exhibit a rich variety of spatio-temporal patterns depending on their rules of evolution. These have found practical applications in modelling, for example, fluid flow, etc.

Discrete models of cell population dynamics of the immune system can be formulated in terms of either "threshold automata" or "Boolean automata" [17].

• **Threshold automata:** The population of the i -th type of cells is denoted by the symbol S_i , where each S_i can take only two possible values: $S_i = 0$ corresponding to a low population and $S_i = 1$ corresponding to a high population. The population of the i -th type of cells at time $t + 1$ is given by the dynamical map [18]

$$S_i(t + 1) = \theta(h_i - \mu_i) \quad (i = 1, 2, \dots, n) \quad (1)$$

where $\theta(y)$ is the step function, i.e., $\theta(y) = 0$ for $y < 0$ and $\theta(y) = 1$ for $y \geq 0$. Moreover, $h_i = \sum_j C_{ij} S_j$ is the total stimulus received by the cells of i -th type, where C_{ij} is the interaction from cell type j to the cell type i and μ_i is a preassigned threshold at which S_i switches from the state 0 to the state 1. The interactions C_{ij} are allowed to take only a few integer values, for example,

$-1, 0, 1$. A specific model is defined by the number n of cell types, the set of values $\{C_{ij}\}$ for all the pairs $\langle ij \rangle$ and the set of values $\{\mu_i\}$ for all i . If $S_i(t+1) = S_i(t)$ for all i simultaneously then the corresponding values of the set $\{S_i\}$ is called a fixed point of the dynamics of the system. On the other hand, if $S_i(t+T) = S_i(t)$ for all i simultaneously, then the system is said to have a limit cycle of period T . The fixed points and the limit cycles are referred to as the attractors of the dynamics.

The concept of *window automata* has also been used extensively in theoretical immunology [19, 20]. Suppose, $S_i = 1$ only if h_i falls within a certain window between two thresholds, i.e., if $\mu' < h_i < \mu''$, and $S_i = 0$ if h_i falls outside this window; then S_i is an example of window automaton.

•**Boolean Automata:** A Boolean automaton is a logical variable which can be only either "true" or "false", usually denoted by 1 and 0, respectively. Therefore, one can describe the cell populations in the discrete models by Boolean variables. However, one cannot carry out the standard algebraic operations, e.g., addition, multiplication, etc., with the Boolean variables. Therefore, if the discrete model is to be formulated in terms of Boolean automata, the dynamical maps will involve logical operations, viz., *OR*, *AND*, *NOT*, etc. For example, if A, B and C are Boolean automata, then

$$\begin{aligned} A &= B.OR.C \text{ is } 1 \text{ if either } B \text{ or } C \text{ or both are } 1 \\ A &= B.AND.C \text{ is } 1 \text{ if and only if both } B \text{ and } C \text{ are } 1 \\ A &= .NOT.B \text{ is } 1 \text{ if } B \text{ is } 0 \text{ and vice-versa.} \end{aligned}$$

The attractors of the dynamics of a Boolean automata network can also be defined just as we did in the case of threshold automata networks.

We now present an illustrative example of a discrete model of NIR, within the framework of the clonal selection scenario, formulated using the language of Boolean automata; this model will be referred to as the e-KUT model as a model of this type was first considered by Kaufman, Urbain and Thomas [21] and extended later by Chowdhury and Stauffer [22, 23]. Suppose, Ab, S, H, B and Ag denote the populations of the antibodies, suppressor T -cells, helper T -cells, B -cells and the corresponding foreign antigen, respectively. In the e-KUT model the dynamical maps governing the population dynamics are given by

$$\begin{aligned} Ab(t+1) &= Ag(t).AND.B(t).AND.H(t) \\ S(t+1) &= H(t).OR.S(t) \\ H(t+1) &= [Ag(t).AND.(.NOT.S(t))].OR.H(t) \\ B(t+1) &= [Ag(t).OR.B(t)].AND.H(t) \\ Ag(t+1) &= Ag(t).AND.(.NOT.Ab(t)) \end{aligned}$$

It is straightforward to check that this model has five fixed points each of which has a bio-medical interpretation. For example, the fixed point corresponding to $Ab = S = H = B = Ag = 0$ is the *virgin* or *tolerant* state whereas the fixed point corresponding to $Ag = Ab = 0$, $H = S = B = 1$ is interpreted as the immunized state where high populations of the lymphocytes carry the memory of the earlier encounter with the foreign antigen to which this clone responds specifically. Although the separate existence of suppressor T -cells is questionable, in the original model of Kaufman et al. [21] a different interpretation of the origin of this suppressing effect was proposed; however, that interpretation has been criticised by Hoffmann[24]. Not only the fixed points of the e-KUT model have interesting bio-medical interpretations, but the sequence of the intermediate states, through which the system evolves from an initial state before reaching the corresponding fixed point, have also been found to be consistent with experimentally known facts.

Chowdhury et al.[23] developed a "unified" model, by generalizing the e-KUT model, which also describes the population dynamics of the cells involved in NIR, AIR as well as NIR against non-HIV antigens in HIV-infected individuals and AIDS. Suppose, the concentrations of the "self-antigen" and HIV are denoted by the symbols IO and IV , respectively, while the concentration of the killer or effector cells involved in the AIR is denoted by the symbol IK . The dynamical maps governing the population dynamics in this model are now postulated to be

$$Ab(t + 1) = Ag(t).AND.B(t).AND.H(t)$$

$$S(t + 1) = H(t).OR.S(t)$$

$$H(t + 1) = [(Ag(t).OR.IO).AND.(.NOT.S(t)).OR.H(t)].AND.(.NOT.IV)$$

$$B(t + 1) = [Ag(t).OR.B(t)].AND.H(t)$$

$$Ag(t + 1) = Ag(t).AND.(.NOT.Ab(t))$$

$$IK(t + 1) = (IO(t).AND.H(t)).AND.(.NOT.S)$$

Cellular-automata models for some other aspects of immune response have also been developed [25, 26, 27].

3.2 Continuum models of clonal selection

Starting from the discrete dynamical equations, written in terms of logical operations among boolean variables, it is possible to derive an analogous system of differential equations of the form

$$(dy_i/dt) = g_i(y_1, y_2, \dots, y_N) - d_i y_i \quad (2)$$

for the n types of cells where y_i and d_i represent, respectively, the concentration and the natural decay rate of the i -th type of cell. The functions g_i involve

combinations of sigmoid functions of y_j 's. Their functional forms can be derived from the form of the right hand side of the corresponding maps in the discrete theories following a well-defined prescription [21, 28]. In order to derive the right-hand side of the differential equation for the concentration y_i from the right-hand side of the corresponding discrete map for the discrete variable S_i : (i) each of the discrete variables S_j is replaced by the corresponding sigmoid function

$$F_i^+(y_j) = y_j^m / (\theta_{ij}^m + y_j^m)$$

whereas each of the discrete variables $.NOT.S_j$ is replaced by the function

$$F_i^-(y_j) = 1 - F_i^+(y_j) = \theta_{ij}^m / (\theta_{ij}^m + y_j^m)$$

where the Hill number m determines the steepness of the sigmoid functions F^+ and F^- and θ_{ij} is the threshold for the regulation of the cell type i by the cell type j ; (ii) the logical operations *OR* and *AND* used in the discrete formulation are replaced by the arithmetic operations of addition (+) and multiplication (\bullet), respectively, in the continuum formulation; (iii) an additional term of the form $-d_i y_i$ (with $d_i > 0$) is introduced to account for the natural decay of the populations of the cells of type i with the passage of time. For example, the differential equation corresponding to the discrete equation

$$S_3 = (S_5.AND.(.NOT.S_2)).OR.S_3$$

is given by

$$(dy_3/dt) = k_3 F_3^+(y_5) \bullet F_3^-(y_2) + k'_3 F_3^+(y_3) - d_3 y_3.$$

Following the prescriptions outlined above, Chowdhury [29] derived the differential equations corresponding to the discrete dynamical maps in the unified model and further simplified the differential equations.

An interesting feature of the NIR in this model is shown in fig.2. Note that a small amount of the antigen is adequate to immunize the host so that it can mount a very strong secondary response against the same antigen even if the antigen dose is high; this captures the essential principle of immunization or vaccination.

Another interesting feature of this model is demonstrated in fig.3. If the host is infected with HIV but the concentration of HIV is low a secondary response to non-HIV antigens can take place despite depletion of the (memory-) T_H -cell populations. On the other hand, no secondary response to non-HIV antigen takes place if the concentration of HIV is sufficiently high. Thus, symptoms of AIDS (namely, lack of response to secondary antigens) would not be visible in an individual already infected by HIV, provided the level of HIV is low.

4 Beyond Clonal Selection; Immune Network:

Clonal selection theory has been very successful in describing many aspects of immune response, but some crucial questions could not be answered so far within the framework of this theory. For example, what makes the memory cells retain their memory? One possibility is that some kind of stimulation of the immune system persists even after the antigen population falls below the tolerance level; in that case memory cells are nothing but cells which are perpetually in a stimulated state. But, if so, what keeps stimulating these cells so selectively and how [30, 31]? Some experiments indicate that persistence of some traces of the foreign antigen after primary response can stimulate the "memory" T - and B -cells [32, 33]. But, although this mechanism may be sufficient, this may not always be necessary as demonstrated by more recent experiments [34, 35].

A possible clue to this mystery of the identity of the specific stimulators, which keeps stimulating a clone so selectively long after the elimination of the foreign antigens, emerges from other sets of experiments. The clonal selection theory, in its classical form, assumed that all immune responses are triggered by antigens. But, it has been observed that in "germ-free" mice (i.e., mice kept for a few generations in environments free from foreign antigens) the number of activated lymphocytes is similar to the values measured in conventionally raised mice [36, 37, 45]. This observation suggests the possibility of stimulating clones also through internal mechanisms. We shall now argue that such internal mechanisms of stimulation follow naturally by going beyond the classical clonal selection theory and invoking the concept of an immune network. This network theory may also explain more satisfactorily some other immunological phenomena, e.g., tolerance and self-nonsel discrimination, etc.

Consider two clones C_1 and C_2 . Suppose, the surface receptors of the lymphocytes and the free antibodies belonging to C_1 and C_2 "fit" with the epitopes of the foreign antigens Ag_1 and Ag_2 , respectively. Therefore, according to the clonal selection theory, C_1 is expected to respond specifically to Ag_1 whereas Ag_2 is expected to stimulate C_2 selectively. It is quite natural to expect that the "molecular pattern" of the receptor molecules, which can recognize "molecular pattern" stored in the epitopes of foreign antigens, can themselves be recognized by others. For example, if the surface receptors of C_1 and C_2 "fit" with each other then C_2 would response to the proliferating lymphocytes of C_1 in exactly the same manner in which it responds against Ag_2 . In other words, C_2 treats C_1 and Ag_2 on the same footing; therefore, C_1 may be regarded as an "internal image" of Ag_2 . An epitope that is unique to the surface receptors and antibodies of a specific type is called an idiotope. Hence, a functional network formed on the basis of idiotope recognition is usually referred to as idiotypic network [38, 39, 40].

Proponents of the immune network theory [41, 42, 43, 44, 45, 46] maintain that the immune response to foreign antigens is offered by the entire immune

system (or, at least, more than one clone) in a collective manner although the dominant role may be played by a single clone whose cell surface receptors "fit" best with the epitope of the specific invading antigen. However, the proliferating cells and antibodies of the responding clone (idiotype) trigger the response of the corresponding anti-idiotypes which, in turn, can stimulate their own anti-idiotypes, and so on. The detailed dynamics of the immune network, of course, would depend on the size and the nature of the connectivity.

- Linear and cyclic networks:* Richter [47] introduced the earliest models of immune networks where a "chain-reaction" of the clones was postulated. Suppose, the clones are such that C_1 stimulates C_2 , then C_2 stimulates C_3 which, in turn, stimulates C_4 , etc. However, this chain reaction is limited by the fact that each clone suppresses the particular clone that was responsible for its stimulation, i.e., simultaneously, suppose, C_4 responds to suppress C_3 , C_3 suppresses C_2 which, in turn, suppresses C_1 . Hiernaux [48] converted the linear chain into a cyclic network and analyzed its properties. Hoffmann and coworkers [49, 50, 51] have made several improvements over the Richter model. Farmer et al. [52, 53] introduced a similar model and compared its features with the other networks used in adaptive computation [54]. This work has been subsequently extended [55, 56] by incorporating memory B-cells. The attractors of the dynamics of such networks can be a limit cycle, where the populations of the antibodies vary periodically and the immunological memory is stored through a combination of "static" elements (namely, long-lived memory cells) and a "dynamic" process, namely, a limit cycle. A discrete toy model of a cyclic immune network has been developed by Chowdhury et al. [57] and its continuum counterpart has been investigated [58].

- Cayley-tree-like network:* A Cayley tree is a loop-less tree characterized by the coordination number z which is the number of branches emerging from each node. In such a network, the clones are organized in a hierarchical manner; the total stimulus received by the B-cells belonging to each of the clones at the i -th level is [59]

$$h^i = x^{(i-1)} + (z-1)x^{(i+1)} \quad (3)$$

where x denotes the concentration of the B-cells. The concentration of the B-cells of the clones at the i -th level are, then, assumed to be governed by window automata (in the discrete formulation) or their continuum counterparts (in the continuum formulation).

- Generalized shape-space approach:* This formulation exploits the fact that the binding affinity of the surface receptors and free antibodies belonging to different clones is determined by the degree of complementarity of their geometric shape, electric charge, etc. Therefore, if the generalized shape (includes d different characteristics) of a clone is represented by a lattice site at \vec{r} in a d -dimensional space then the location of its anti-idiotype should be $-\vec{r}$ on the same d -dimensional lattice (see fig.4). Thus the strength of the interaction between the clones at the lattice site \vec{r} and $-\vec{r}$ is maximum. Moreover, since the

clone at \vec{r} has still significant amount of complementarity in generalized shape with the nearest-neighbour sites of $-\vec{r}$ the clone at the site \vec{r} is usually assumed to interact also with those at the sites $-\vec{r} \pm \vec{\delta}_x$ and $-\vec{r} \pm \vec{\delta}_y$, although these interactions are much weaker than that between \vec{r} and $-\vec{r}$ [60, 61, 62, 46, 63, 64]. It is desirable that if the virgin system is infected by a single specific antigen that the response activities should remain confined over a limited region of the generalized shape space in spite of the fact that the entire network is connected. After all, when a person gets infected by tuberculosis he is not expected to show large populations of antibodies against cholera! It has been found that the dimensionality of the generalized shape space determines whether the response activities remain localized or percolate over the entire network.

Chowdhury et al. [57] have extended the e-KUT model [22, 23] of clonal selection so as to incorporate explicitly both intra-clonal and inter-clonal interactions. They postulated that the immune system in a host consists of several functional networks of various different sizes; clones belonging to different networks do not interact among themselves and only clones belonging to the same network can interact among themselves through inter-clonal interactions. For example, on a square lattice the dynamical maps governing the time evolution of the populations of the various cell types are given by

$$\begin{aligned}
Ab(\vec{r}, t+1) &= Ag(\vec{r}, t).AND.B(\vec{r}, t).AND.H(\vec{r}, t) \\
B(\vec{r}, t+1) &= [Ag(\vec{r}, t).OR.H(-\vec{r}, t).OR.H(-\vec{r} + \vec{\delta}_1, t).OR.H(-\vec{r} + \vec{\delta}_2, t) \\
&\quad .OR.H(-\vec{r} + \vec{\delta}_3, t).OR.H(-\vec{r} + \vec{\delta}_4, t)].AND.H(\vec{r}, t) \\
H(\vec{r}, t+1) &= [Ag(\vec{r}, t).OR.H(-\vec{r}, t).OR.H(-\vec{r} + \vec{\delta}_1, t).OR.H(-\vec{r} + \vec{\delta}_2, t) \\
&\quad .OR.H(-\vec{r} + \vec{\delta}_3, t).OR.H(-\vec{r} + \vec{\delta}_4, t)].AND.[.NOT.[H(-\vec{r}, t).AND.H(-\vec{r} + \vec{\delta}_1, t) \\
&\quad .AND.H(-\vec{r} + \vec{\delta}_2, t).AND.H(-\vec{r} + \vec{\delta}_3, t).AND.H(-\vec{r} + \vec{\delta}_4, t)]] \\
Ag(\vec{r}, t+1) &= Ag(\vec{r}, t).AND[.NOT.Ab(\vec{r}, t)]
\end{aligned}$$

where $\vec{r} + \vec{\delta}_1, \vec{r} + \vec{\delta}_2, \vec{r} + \vec{\delta}_3, \vec{r} + \vec{\delta}_4$ denote the positions of the four nearest-neighbours of the site \vec{r} . Thus, every clone at \vec{r} can stimulate not only the anti-idiotypic at $-\vec{r}$ but also those clones which are located at the nearest-neighbour sites of $-\vec{r}$. On the other hand, so far as suppression is concerned, the high population of the clone at \vec{r} can be reduced to a low level if and only if the populations of the clone at $-\vec{r}$ and the clones at the latter's $2d$ neighbouring sites are high simultaneously. Therefore, on the one hand, mutual stimulation is symmetric in the sense that the clone at \vec{r} excites the clone at $-\vec{r}$ and vice versa. On the other hand, mutual suppression is also symmetric in the sense that clones at \vec{r} and its $2d$ neighbouring sites together can reduce the population of the clone at $-\vec{r}$ and, similarly, the clones at $-\vec{r}$ and its nearest-neighbours can reduce the high population of the clone at \vec{r} to a low level. However, there is asymmetry between stimulation and suppression because suppression succeeds

only if the entire neighbourhood of the antiidiotype, rather than the antiidiotype alone, is highly populated. Chowdhury et al.[57] observed that, in this model, once a site of the shape space is infected a pulse propagates and the pattern of the pulse keeps recurring for ever, thereby carrying the memory of the encounter with the foreign antigen through a dynamic mechanism.

5 Summary and Conclusion:

The immune system is an example of complex adaptive systems. Other important adaptive systems include the brain (neural network) [65]. There are several striking similarities between the brain and the immune system despite many crucial differences. Adaptive systems learn or adapt as living systems do. Different systems learn on widely different time scales; for example, brains learn in seconds to hours, immune systems in hours to days, species in days to centuries and ecosystems in centuries to millenia. In my opinion, there are at least two different aspects of the dynamics of the immune system: (a) the populations of the cells of a specific clone (and, perhaps, closely related clones) increase very rapidly following the recognition of any foreign antigen and, after the elimination of the antigen, decrease again; (b) because of the natural death of unstimulated lymphocytes and recruitment of fresh immunocompetent cells the immune network itself evolves with time and all its characteristic properties, e.g., size, connectivity, etc., may also keep changing with time. Both the processes (a) and (b) occur on comparable time scales. Therefore, inclusion of both these aspects in the same model is more desirable than studying the cell-population dynamics in a network of fixed size and connectivity. In fact, not only the later evolution but also the formation of the immune network in a newborn child is a challenging problem. Even the size and the connectivity of the immune system may be among its emergent collective properties [66]. It has been speculated [67] that immunological memory would be much more robust if it is distributed over many clones rather than a single one.

In this chapter we have not only explained some interesting methods of modelling in theoretical immunology but also presented some models as illustrative examples. Even if some of these models turn out to be inadequate to capture the complexities of the real immune system they may, nevertheless, find use in designing artificial immune systems for the protection of information systems (e.g., computer, internet, etc.) against the corresponding "antigens" (e.g., computer virus and internet worms, etc.).

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Figure Captions:

Fig.1: A schematic description of the routes to immunity.

Fig.2: The time-dependence of the population of the antibodies during the primary and secondary NIR for different antigen-dosages. The primary and secondary doses are given at $t = 0$ and $t = 100$, respectively. The strengths of the primary and secondary doses of antigen are both 1 (in (a)), 10 (in (b)), 100 (in (c)) whereas those of the antigen are, respectively, 1 and 100 (in (d)).

Fig.3: The time-dependence of the helper-T cells (full line), suppressor-T cells (dashed line), the antibodies (dotted line) and the antigen (asterisk-marked line) of a host, which has been immunized first against a specific non-HIV antigen, during an infection by different levels of HIV dose and the subsequent secondary response. The HIV dose is given at $t = 0$ and the secondary dose of the non-HIV antigen is given at $t = 150$ where the strength of the secondary dose of the non-HIV antigen is 5. The levels of HIV doses are 0.5 (in (a)), 1.5 (in (b)) and 5.0 (in (c)).

Fig.4: A schematic representation of the two-dimensional generalized shape space.







